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(54) Title: PREPARATION OF STERILE AQUEOUS SUSPENSIONS COMPRISING MICRONISED CRYSTALLINE ACTIVE INGREDIENTS FOR INHALATION

(57) Abstract: Disclosed is a process for the preparation of sterile aqueous suspensions based on active ingredients in the form of micronised crystalline particles designed for administration by inhalation. In particular, a process for the preparation of sterile aqueous suspensions based on pharmaceutical active ingredients in the form of crystalline hydrates is disclosed.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

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This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.



the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International search was carried out on the basis of the sequence listing:



contained in the International application in written form.



filed together with the International application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

PREPARATION OF STERILE AQUEOUS SUSPENSIONS COMPRISING MICRONISED CRYSTALLINE ACTIVE INGREDIENTS FOR INHALATION

INTERNATIONALER RECHERCHENBERICHT

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

PREPARATION OF STERILE AQUEOUS SUSPENSIONS COMPRISING MICRONISED CRYSTALLINE ACTIVE INGREDIENTS FOR INHALATION

This invention relates to a process for the preparation of sterile aqueous suspensions based on micronized crystalline active ingredients designed for delivery by inhalation.

BACKGROUND OF THE INVENTION

5 The method of delivering drugs by inhalation has been used for several years, and is the mainstay of the treatment of disorders which limit the respiratory flow, such as asthma and chronic bronchitis.

The advantages of inhalation over the systemic route include the fact that the drug is released directly at the site of action, thus preventing systemic
10 side effects and resulting in a faster clinical response and a higher therapeutic index.

These advantages have also been used in the pulmonary administration of drugs designed to produce a systemic effect in the treatment of non-pulmonary disorders. Drugs administered by the inhalation route are dispensed
15 in the form of powders by powder inhalers, as solutions or suspensions in fluorinated propellant by pressurized metered dose inhalers (MDI), or as aqueous solutions or suspensions by suitable ultrasound or compressed-air nebulisers. These drugs belong to different therapeutic classes: they are represented in particular by drugs designed for the treatment of respiratory
20 diseases, such as antibiotics, corticosteroids, mucosecretolytics, anticholinergics and β_2 -adrenergic receptor agonists.

The aerosol therapy is mainly used to treat inflammatory disorders; in this field, a special place is held by corticosteroids such as beclomethasone dipropionate (BDP), mometasone furoate, flunisolide, budesonide, ciclesonide

and fluticasone propionate. These drugs are generally administered in micronised form in suspension in an aqueous vehicle or in a propellant. The drug is inhaled in aerosol form, i.e. in the form of a dispersion of solid particles in a gaseous medium. The efficacy of this form of administration depends on the deposit of a sufficient amount of particles at the site of action.

If peripheral areas of the respiratory tree, such as the alveoli, are to be reached, as in the case of bronchopulmonary formulations, one of the most important parameters is the particle size, which must be lower than or equal to 5-6 micron. This size is quantified by measuring a characteristic sphere-equivalent diameter, known as the median aerodynamic diameter (MAD), which expresses the ability of particles to be transported in suspension in an airstream. Another parameter widely utilised is the mass median aerodynamic diameter (MMAD) which corresponds to the MAD of the 50 percent by weight of the particles.

Particles with a larger MAD are ineffective, because they are deposited in the oropharyngeal cavity, and are therefore unable to reach the terminal branches of the respiratory tree. They can also give rise to local side effects, or may be absorbed through the mucous membranes and give rise to systemic side effects.

Particles of suitable size for inhalation treatment are not generally obtainable by simple crystallisation from a solution. In order to obtain high crystallinity and adequate purity, and to minimise the residual solvent content, products for pharmaceutical use are crystallised slowly; however, particles with a non-uniform size which exceeds the upper limit specified above are normally produced under these conditions. On the other hand, in order to obtain a fine precipitate, the crystallisation process must be rapid but in this case it is very difficult to identify the relevant parameters such as solvent, concentration, temperature and time, so as to obtain a completely crystalline

product and/or avoid the inclusion of impurities in the crystals. Products designed for inhalation therefore normally undergo a micronisation treatment. This treatment is usually performed in a fluid energy mill constituted by a chamber with a circular or other geometrical shape (e.g. a flattened ring), with
5 a lateral extension into which the active ingredient to be micronised is introduced. A fluid, generally air or nitrogen, is injected at high pressure through nozzles in the bottom of the unit. The solid material is introduced into the fluid stream, and as a result of the high turbulence created, develops friction and impact between particles and between the particles and the
10 chamber walls, which leads to a reduction in their size. A centrifugal classifier (cyclone) is incorporated into the apparatus so that the particles are retained until they reach the desired degree of fineness. Solid materials, especially steroids, usually contain particles with sizes of up to 150 micron before being micronised. In order to obtain particles of suitable dimensions for pulmonary
15 administration (5-6 micron), the parameters involved (fluid pressure, chamber temperature, time of solid material addition and micronisation time) must be regulated on the basis of the characteristics of the active ingredient (initial size, and hardness of crystal). In general, the larger their size and the harder the crystal, the more time the particles must remain in the micronisation
20 chamber, and/or the higher the flow rate and pressure of the fluid used need to be. The micronisation of steroids such as BDP is usually conducted at a pressure of between 10 and 12 bar, for approx. 30 minutes.

However, micronisation techniques have some drawbacks, including the fact that the percentage of particles obtained having the desired particle size
25 may be relatively small. The yield of the process can also be relatively low (considerable loss of product can be caused by its adherence to the walls of the apparatus used). Another disadvantage is that in the case of solvated products, the conditions used can cause loss of solvent, with a change in the

crystalline structure and consequent formation of polymorphs. Another undesirable characteristic of micronised products is that the surface of the particles generated is often mainly amorphous, so that they tend with time to be converted into the more stable crystalline state, which may be different
5 from the original state. The harder the conditions and the longer the micronisation time, the greater the degree of amorphisation. This drawback is particularly significant in the case of active ingredients which need to be resuspended in water. Materials which are even only partly amorphous are more liable than crystalline materials to moisture uptake (Hancock et al. *J. Pharm. Sci.* 1997, 86, 1-12), and this has adverse effects on active ingredients
10 whose chemical stability is particularly sensitive to the humidity content.

Another drawback of micronisation processes is that they require high energy and therefore require containment and other measures to avoid the risk of explosion.

15 Another problem which may affect micronised products, when formulated as suspensions, is an increment of the particle size over time as a result of total or partial recrystallisation of the small quantity of dissolved solute (Davis et al *Int J Pharm* 1, 303-314, 1978; Tiano et al *Pharm Dev Tech* 1, 261-268, 1996; Taylor et al *Int J Pharm* 153, 93-104, 1997). Such an
20 increase can prejudice the efficacy of nebulisation and therapeutic efficacy because, as stated, particles with an MAD exceeding 5-6 μm are unable to reach the preferential site of action.

The phenomenon of 'crystalline growth' has been observed in particular for some steroids, such as BDP and flunisolide. When these active ingredients
25 are formulated in suspension in inhaler propellants or aqueous vehicles, the crystals grow, leading to the formation of particles with a greater particle-size distribution than the original one. Another important requirement that must be met by pharmaceutical formulations designed for pulmonary delivery is

sterility. This requirement is more and more recommended in various documents dealing with quality and safety of pharmaceutical products for a number of reasons, including the fact that the lungs are a particularly vulnerable organ of the human body, and many patients who use inhaled drugs have general health problems. The current trend is to produce inhalation formulations devoid of preservatives and bacteriostatics, as it has been reported in the literature that some of the substances commonly used for this purpose can give rise to allergic reactions or irritate the respiratory mucosae (Menendez R *et al J Allergy Clin Immunol* 84, 272-274, 1989; Afferty P *et al Thorax* 43, 446-450, 1988). Various processes can be used to manufacture sterile pharmaceutical formulations for inhalation. For example, the active ingredient can be pre-sterilised by dry heating or radiation, followed by preparation of the formulation under aseptic conditions as reported in WO 99/25359 and WO 00/25746, or the formulation can be pre-prepared and sterilised by treatment in an autoclave.

However, all the sterilisation methods reported for aqueous suspensions suffer from drawbacks or limitations. For example, pre-sterilisation methods require a subsequent stage of mixing of the active ingredient thus obtained with the other ingredients of the formulation, and preparation of the final formulation under aseptic conditions till the introduction into the final sterile container. Standard autoclaving treatments are unsuitable for aqueous suspensions of thermolabile corticosteroids (such as BDP), because they cause the chemical degradation of the active ingredient. These treatments can also give rise to agglomerates of particles of the active ingredient in the suspension which are difficult to redisperse, thus jeopardising their therapeutic efficacy. Finally, in the case of suspensions, sterilising filtration is not feasible because it requires the use of filters with a pore size less than or approximately equal to 0.2 micron, not compatible with the size of the dispersed particles.

Various prior publications specifically refer to processes for obtaining active ingredients for pulmonary administration in a crystalline form by crystallisation from a solution in a suitable solvent upon addition of a proper anti-solvent.

5 GB 2107715, filed by Glaxo, describes the preparation of BDP monohydrate for use in the preparation of pharmaceutical compositions in dry powder form. The text states that BDP monohydrate can be prepared by crystallisation by slowly adding a solution of BDP in a water-miscible organic solvent, which may be ethanol, to water. After crystallization, the
10 monohydrate may be isolated by, for example, filtration and washed and dried in conventional manner. The beclomethasone dipropionate monohydrate is then micronized to the desired particle size range by conventional techniques, for example using a ball mill or fluid energy mill or by ultrasonic means.

At least 90% in weight of the particles obtained are under 10 micron in
15 size, and preferably 2-5 micron. The active ingredient is then formulated as a dry powder in a mixture with conventional solid diluents.

There is no teaching about how to make a sterile crystalline BDP monohydrate and/or pharmaceutical compositions in form of aqueous suspension for pulmonary delivery wherein the particle size distribution of the
20 crystalline active ingredient does not change.

In the prior art, BDP monohydrate was only used to prepare suspensions in fluorinated propellants, to be delivered by metered dose inhalers, which do not need to be sterilised (patent applications WO 93/15741, WO 96 32345 and WO 99/53901 filed by Glaxo). Otherwise, BDP monohydrate has been used to
25 prepare aqueous suspensions for nasal administration which are not sterile, and in order to be effective at the nasal mucosa level normally contain particles with a MAD greater than 10-20 micron, as proposed in the FDA guideline "Bioavailability and Bioequivalence Studies for Nasal Aerosols and

Nasal Sprays for Local Action" issued in June 1999.

WO 90/03782, filed by the Upjohn Company, describes a process for the preparation of finely divided solids which involves dissolving the solid in a suitable solvent and adding the solution to an anti-solvent chosen from the group of supercritical fluids, compressed gases or condensed vapours. The preferred anti-solvent is carbon dioxide, while the solvent should be chosen according to the type of active ingredient.

US 5314506, filed by Merck, claims a process for crystallisation of an organic pharmaceutical compound which comprises contacting one or more jet streams of a feed solution of the compound with one or more jet streams of an anti-solvent in conditions of high turbulence and with sufficient linear velocity to produce crystals with a diameter equal to or less than 25 micron. One of the jet streams optionally includes a surfactant, to prevent agglomeration of the particles.

WO 96/32095, filed by Astra, discloses a process for producing a pharmaceutical powder for inhalation with crystalline particles having a diameter of less than 10 micron which involves preparing a saturated or supersaturated solution of active ingredient and causing it to collide, in the form of a jet stream or droplets obtained through a nozzle or porous filter, with an anti-solvent under agitation. Methanol, isopropanol, dimethylsulphoxide, dimethylformamide and others can be used as organic solvents in the case of water-insoluble active ingredients. The text states that the process preferably takes place at a low temperature (below 25°C, and preferably between 0 and 5°C). The examples refer to budesonide.

US 5314506 and WO 96/32095 require isolation of the products before preparation of the final formulation, and are therefore incompatible with a continuous production process. The applicant has also demonstrated that due to the Venturi effect, the delivery of a solution as a spray through a nozzle

leads to cooling of the organic solution, which in turn can cause crystallisation of the active ingredient and clogging of the nozzle under supersaturated conditions.

In WO 00/25746, filed by the the applicant, aqueous suspensions for
5 nebulisation based on a micronised steroid designed for inhalation, sterilised with gamma rays are described. The process basically involves a first stage of preparation in a turboemulsifier of an aqueous solution which constitutes the vehicle and contains suitable excipients, followed by the addition of the sterile
10 micronised active ingredient and its dispersion at atmospheric pressure in the same turboemulsifier. The dispersion of the active ingredient in the aqueous phase may be subjected to an additional high-pressure homogenising treatment which further reduces the average size of the particles in suspension. The examples refer to BDP.

WO 01/49263, filed by Orion, relates to a process which involves: i)
15 preparing a solution or suspension of active ingredient; ii) atomising it to create droplets; iii) suspending said droplets in an inert gas which acts as carrier gas; iv) passing them through a heated tube flow reactor; v) collecting the particles with conventional techniques.

The invention is designed for active ingredients delivered by inhalation,
20 with crystalline, spherical, rough, uncharged particles. This process is incompatible with a continuous production process. The passage through a tube flow reactor also involves a heating stage, which may not be compatible with thermolabile substances such as some steroids designed for inhalation.

WO 00/53282, filed by Smithkline Beecham, discloses a process for the
25 continuous crystallisation of an organic compound which involves contacting a solution of active ingredient with an anti-solvent or colder solvent, or a suitable solution of an acid or base, and separating the crystals formed. The process preferably takes place in conditions of turbulence, and precipitation

preferably takes place in less than 1 minute, and even more preferably in less than 5 seconds. The examples relate to eprosartan methanesulphate and nabumetone, two active ingredients unsuitable for administration by inhalation. For the former, the preferred solvent is acetic acid and the preferred anti-solvent is tert-butyl methyl ether or ethyl acetate. For the second active ingredient, the preferred solvent is 2-propanol, and the preferred anti-solvent is water.

WO 01/14036, filed by Aventis, claims a method for the preparation of drug particles which involves: i) dissolving the active ingredient in a solvent; ii) collision with an anti-solvent under conditions of turbulence followed by rapid precipitation of the active ingredient in the form of crystalline particles with a controlled diameter. This process is characterised in that the velocity of the opposing streams must exceed 50 m/sec, the ratio between anti-solvent volume and solvent volume must be $> 2:1$ (preferably between 15:1 and 30:1), and the angle of collision between the two streams must preferably be less than 20 degrees. The invention is designed to produce drugs for inhalation with a final diameter of between 2 and 5 micron. Triamcinolone acetonide is indicated as the preferred active ingredient. There is no teaching relating to obtaining a sterile product, and in any event the process is incompatible with a continuous production process.

Various patent applications filed by Glaxo (WO 00/38811, WO 01/32125, WO 02/00198 and WO 02/00199) relate to processes for the preparation of crystalline particles of a substance which comprises the following stages: i) mixing a solution of active ingredient with an anti-solvent in a continuous-flow cell to generate a suspension; ii) filtering the suspension so as to isolate the particles with a diameter of between 1 and 10 micron, and preferably under 5 micron; iii) isolating and collecting the particles using techniques such as freeze-drying. In particular, the applications relate to

conditions of isolation of the products (and consequently elimination of the solvents) which prevent crystalline growth of the particles during the isolation process.

The examples refer to fluticasone and salmeterol.

5 In WO 00/38811 and WO 02/00199 it is expressly stated that when the active ingredient is BDP, industrial methylated spirits (IMS) will preferably be used as organic solvent.

Here again, unlike the present invention, the processes always involve isolation of the products before preparation of the final formulation, and are
10 therefore incompatible with a continuous production process.

In view of all these drawbacks, it would be a great advantage to provide a process which overcomes or at least mitigates the limitations of the technical solutions proposed in the prior publications.

SUMMARY OF THE INVENTION

15 A process for the preparation of sterile aqueous suspensions for nebulisation, which comprise a micronised active ingredient insoluble in water, has now been found. Said process comprises the following steps :

- i) a solution of the active ingredient in an organic solvent is prepared in a suitable reactor (A);
- 20 ii) said solution is sterilised by filtration;
- iii) in parallel, a sterile aqueous phase containing pharmaceutically acceptable excipients is prepared in a turboemulsifier (B);
- iv) the sterile organic solution ii) is added in a suitable reactor (C) to the sterile aqueous phase iii) to yield the active ingredient in
25 crystalline form so forming a sterile suspension;
- v) the organic solvent is eliminated;
- vi) the suspension is filled in suitable containers under sterile conditions.

The temperature of the organic solution is preferably between 25 and 80°C, preferably between 40 and 70°C, and that of the sterile aqueous phase between 5 and 50°C, preferably between 10 and 25°C.

One of the advantages of the process according to the invention is that
5 the active ingredient is sterilised by simple filtration through sterilising filters avoiding heating or irradiation.

A further advantage is that said process can produce particles with a controlled particle size distribution, preferably with a MMAD lower than 6 micron which is suitable for products administered by pulmonary inhalation.

10 Moreover, the process of the invention allows continuous processing without separation of the intermediate products; all stages of the process take place at room temperature, can be conducted without contact with air, and are therefore compatible with manufacture in aseptic conditions.

Hereafter, the term "solvent" is used to mean the medium in which the
15 active ingredient is dissolved, and "anti-solvent" to mean the medium in which its precipitation takes place, and which determines the crystalline characteristics of the product.

The anti-solvent of the present invention is always water.

As excipients, pharmaceutically acceptable ingredients commonly used
20 for the preparation of aqueous suspension formulation are used. In particular, it is preferable for wetting agents to be present in the water that acts as anti-solvent.

It has been found that the presence of wetting agents at the crystallisation stage promotes the formation of the hydrated form of particular
25 kinds of active ingredients, namely a physically stable form which does not give rise to crystalline growth once in suspension in water, without altering their characteristics of purity and the degree of crystallinity.

In a particular embodiment of the invention the active ingredient is

further subjected to a wet micronisation treatment in a high-pressure omogeneizer (H), without prior isolation of the product, to give rise to an even better distribution of the particle size of the active ingredient, with a MMAD lower than or equal to 3 to 4 micron. Said treatment is not only bland, but also
5 eliminates the problems associated with dry micronisation, as the particles are uniformly dispersed in the aqueous vehicle.

The process of the invention can also envision isolation and collection of the active ingredient particles, after addition of the anti-solvent to the organic solution in reactor (C), by filtration under sterile conditions, followed
10 by a reduction in the particle size of the active ingredient by dry micronisation in a fluid energy mill (D) operating in a sterile environment.

The micronised active ingredient thus obtained is then dispersed in a turboemulsifier (B) in which a pre-sterilised aqueous solution containing the excipients has been prepared. The filling in suitable container under sterile
15 conditions completes the process.

In fact, it has been found that the particles of active ingredient, obtained after addition of the anti-solvent according to the process of the invention, can easily be isolated by filtration under sterile conditions without clogging the filter. Said particles, by virtue of their particle-size distribution, can be
20 micronised in the fluid energy mill at lower operating pressures (5-6 bar) than those normally used (10-12 bar) that could prejudice or alter their crystalline state. The use of bland conditions also allows to reduce the flow rate of the high-pressure fluid (sterile air or nitrogen), thereby lowering the costs.

A further aspect of the present invention relates to aqueous suspensions
25 of micronised crystalline active ingredients obtained with the claimed process, for delivery by inhalation. Particularly preferred are sterile formulations in the form of aqueous suspensions designed for pulmonary delivery of corticosteroids for the treatment of respiratory disorders such as asthma and

chronic bronchitis.

An even more preferred sterile formulation comprises crystalline particles of BDP monohydrate wherein the volumetric diameter of at least 90% of the suspended particles is less than or equal to 10 micron, preferably 8 micron, more preferably 6 micron.

DETAILED DESCRIPTION OF THE INVENTION

The characteristics of the process and the pharmaceutical compositions of the invention will be described in greater detail below. Process diagrams are shown in Figures 1 and 2. The process of the invention can advantageously be applied to active ingredients which are insoluble or poorly soluble in water as defined in the European Pharmacopoeia Ed. 4th, 2003, page 2891 and can be delivered to the lungs by inhalation in the form of aqueous suspensions. Preferred active ingredients are antibiotics and corticosteroids such as BDP and budesonide and its epimers, flunisolide, mometasone furoate, ciclesonide, rofleponide, triamcinolone acetonide and fluticasone propionate, useful for the treatment of respiratory diseases. In a particular embodiment, the active ingredients will give rise to hydrated forms which do not undergo crystalline regrowth in an aqueous suspension, such as flunisolide hemihydrate, amoxicillin and ampicillin trihydrate, cefaclor, cefadroxil and cephalixin monohydrate.

Preferred active ingredients are thermolabile corticosteroids. Even more preferably the active ingredient is beclomethasone dipropionate which, after crystallisation in the presence of water, gives rise to the monohydrated form.

BDP monohydrate can be characterised by X-ray diffractometry on the powders by exposure to Cu K α radiation.

The angles ($\pm 0.1^\circ/2\phi$) and relative intensities of the peaks (in brackets) are set out below (the intensity may change on variation of the powder packing conditions):

8.2 (85); 9.1 (13); 9.5 (12); 11.0 (21); 12.5 (39); 13.0 (13); 13.5 (6);
14.5 (100); 15.5 (20); 15.9 (20); 16.8 (25); 17.4 (16); 18.1 (22); 19.0 (23);
20.5 (11); 20.9 (9); 21.8 (19); 22.2 (14); 22.9 (18); 23.5 (11); 23.8 (18); 24.5
(13); 25.4 (14).

- 5 The monohydrate can be also characterised by means of its infrared (IR) spectrum. The principal absorption bands are reported below:

3560 cm^{-1} (vs); 3510 (s); 3300 (vs); 1730 (vs); 1663 (s); 1630 (m);
1285 (m); 1190 (vs); 1120 (m); 1090 (vs); 1053 (m); 973 (m); 940 (m)
(vs = very strong; s = strong; m = average).

- 10 Finally, the monohydrate can be characterised by means of thermal analysis. After scanning from 50°C to 350°C at 15°C/min, the thermogram must show an endothermal peak between 100 and 140°C (with the maximum at approx. 120°C) corresponding to the loss of water of crystallisation followed by the melting endotherm of BDP at approx. 218°C.

- 15 Advantageously, the concentration of active ingredient in the final suspension is between 0.001 and 1% w/v, and preferably between 0.02 and 0.1% w/v. In the case of BDP monohydrate, the preferred concentration is 0.04% w/v.

- 20 The filtration through sterilising filters requires prior dissolution of the active ingredient in an organic solvent in a reactor equipped with a stirring system (A in figures 1 and 2). Various parameters must be evaluated in order choose the solvent with the most suitable properties: the solubility and stability of the active ingredient in said solvent, its miscibility with water, and the characteristics of toxicity, volatility and corrosiveness towards the walls of
25 the apparatus. In general, the organic solvent must have a high solubilising capacity for the active ingredient, low toxicity and a low boiling point, must not be corrosive for the apparatus, must be able to form azeotropes with water with a high solvent content, and must preferably be miscible with water.

The solvent is advantageously selected from the group that comprises ethanol, acetone, methyl ethyl ketone and ethyl acetate. The solvent is preferably ethanol. Said solvents guarantee in particular a good solubility of corticosteroids, give solutions that are stable for at least two hours at 40°C, have a low boiling point (under 80°C), are not corrosive, have low toxicity, and are miscible with water at the volume ratios used in the processes of this invention.

In the case of BDP, it has been found that when ethanol is used, the solid particles of BDP monohydrate immediately precipitate in crystalline form, whereas when acetone or ethyl acetate is used, BDP monohydrate first tends to separate in an amorphous, almost pitch-like form, which adheres to the walls of the container and then crumbles, subsequently giving a crystalline solid.

The type of filter employed to sterilise the solution will be chosen on the basis of the organic solvent used, and the porosity of said filter will necessarily be not more than 0.22 micron, preferably 0.2 micron, and even more preferably 0.1 micron. Nylon, Durapore or Teflon filters could advantageously be used. The preferred material is Nylon 66. The sterilising filtration is preferably performed under pressure.

A turboemulsifier operating under vacuum, constituted by a steel container fitted with a jacket with a cavity wall suitable for steam heating and with a turbine and/or agitation system (B in figures 1 and 2), could advantageously be used as the reactor in which the aqueous solution constituting the vehicle of the final formulation is prepared. The aqueous solution may contain the pharmaceutically acceptable ingredients commonly used for the preparation of aqueous suspensions, i.e. wetting agents such as polysorbate 20, polysorbate 80 or sorbitan monolaurate, isotonicity agents such as sodium chloride, and possibly stabilisers such as disodium edetate

and/or buffer agents. The vehicle can be pre-sterilised by heat or filtration, preferably by heating at 121°C for 20 minutes.

The active ingredient will be crystallised by adding the organic solution to the aqueous phase in a suitable reactor equipped with a stirring system and
5 loading cells (C in figures 1 and 2). The reactor can be fitted with an internal filter, as shown in figure 2.

In order to crystallise the active ingredient with the desired particle size distribution, the concentration of active ingredient in the organic solvent is advantageously between 2 and 30% w/v, and preferably between 5 and 25%
10 w/v. The temperature of the solution, under supersaturated conditions, will be regulated so as to prevent recrystallisation of the active ingredient, and will preferably be between 25°C and 80 °C, more preferably between 40 and 70°C. The volume of the organic solution added will be much smaller than the aqueous solution constituting the vehicle, and the two solutions will
15 preferably be in a ratio of between 0.001 and 0.02 v/v, and even more preferably between 0.005 and 0.01 v/v.

The time taken to add the organic solution to the aqueous solution will advantageously be between 1 and 20 minutes, and preferably between 2 and 10 minutes. The aqueous solution will preferably be maintained under stirring.

20 The temperature of the aqueous phase to which the organic solution is added will advantageously be maintained at between 5 and 50°C, and preferably between 10 and 25°C, for a time of between 5 minutes and 3 hours, preferably between 30 minutes and 2 hours, and even more preferably for a time less than or equal to 30 minutes.

25 In the case of BDP monohydrate, the best particle size distribution is obtained by operating at about 10°C.

In a preferred embodiment of the invention (Figure 1), the aqueous solution will contain all the excipients constituting the final formulation. In

particular, it is preferable for wetting agents such as polysorbate 20, sorbitan monolaurate or their mixture to be present. This also allows rapid formation of the hydrated forms of particular active ingredients, even with relatively short addition times which are suitable for the formation of particles with a fine
5 enough size. At the end of the crystallisation stage, the $d(v,0.9)$ of the particles in suspension, ie. the volumetric diameter below which 90% of the particles fall, will advantageously be less than or equal to 70, preferably 60, more preferably 50 micron, even more preferably less than or equal to 30 micron, as determined by laser diffraction (Malvern) after sonication; the
10 $d(v,0.5)$, i.e. the volumetric diameter below which 50% of the particles fall (MMAD), will be of about 20 micron, preferably equal to 10 micron, and the $d(v,0.1)$, ie. the volumetric diameter below which 10% of the particles fall, will be less than or equal to 4 micron.

In the process shown in figure 1, the organic solvent can be removed
15 after addition of the organic solution to the aqueous vehicle by evaporation under vacuum and heating. Advantageously, the evaporation will be conducted at 40-60°C for a time of between 30 minutes and 3 hours. If a reduction in water content is also observed during this operation, the suspension will be made up to volume so as to readjust the active ingredient assay.

Alternatively, the organic solvent can be removed by diafiltration. The
20 suspension is circulated through a system of filters (E) installed in parallel to the reactor in which crystallisation takes place until the desired residual quantity of organic solvent is obtained; at the same time, the reactor is fed with pre-sterilised water to keep the volume, and therefore the assay of the
25 active ingredient constant. This operation reduces the residual content of organic solvent to values less than or equal to 1000 ppm of the total weight of the formulation.

The wet micronisation treatment is performed in a high-pressure

homogenizer (H). By exploiting very high pressures, up to 1500 bar corresponding to 0.015 Pascal (1 bar equal to 10^{-5} Pascal), this apparatus reduces the size of the suspended particles and disperses them evenly by forced passage of fluid at high pressure and turbulence through a suitable valve. The extent to which the size of the suspended particles is reduced depends on the operating pressure and the shape and dimensions of the micronisation chamber. Advantageously, the suspended particles will be treated at an operating pressure of between 100 and 1000 bar (0.001–0.01 Pascal) for one or more cycles of treatment, preferably between 150 and 800 bar (0.0015–0.008 Pascal); even more preferably, the particles will be treated at 600 bar (0.006 Pascal) for a single cycle of treatment.

This operation restricts the particle-size distribution curve so that the volumetric diameter of at least 90% of the suspended particles is less than or approximately equal to 10 micron, preferably of about 6 micron. Advantageously, the volumetric diameter of at least 50% of the suspended particles will be less than or approximately equal to 6 micron, and preferably of approximately 3 to 4 micron, and the volumetric diameter of at least 10% of the suspended particles will be less than or approximately equal to 2 micron. The particles obtained at the end of the crystallisation stage can also be isolated by filtration, dried and loaded into a fluid energy mill (D in Figure 2). The filtration stage can take place either outside or inside reactor C. In the mill, a fluid, generally air or nitrogen, is injected at high pressure through nozzles in the bottom of the unit. The solid material is introduced into the fluid stream and, as a result of the high turbulence created, forces of friction and impact between the particles are generated.

Advantageously, the pressure of the fluid stream is lower than 12 bar, preferably is comprised between 5 and 6 bar. The preparation of the final formulation from the sterile micronised particles thus obtained is carried out

under aseptic conditions, preferably according to the teaching of the International patent application no. WO 03/086347.

The micronised suspension is distributed, under aseptic conditions, in suitable containers constituted by multidose, or preferably monodose vials, which are pre-formed or made with the "blow, fill and seal" technology.

The invention is illustrated in greater detail in the example below.

EXAMPLES

Example 1 - Preparation of a sterile aqueous suspension based on 0.04% (w/v) BDP monohydrate

Composition:

Ingredients	Total quantity of the preparation	Quantity by unit dose
Sterile micronised BDP monohydrate	6 g	(0.8 mg)
Polysorbate (Tween) 20	15 g	(2.0 mg)
Sorbitan monolaurate	3 g	(0.4 mg)
Sodium chloride	135 g	(18.0 mg)
Water for injection q. s. for	15 l	(2.0 ml)

The first stage of preparation of the sterile suspension involves preparing a solution to be subjected to sterilisation by filtration. For this purpose, 6 g of BDP was dissolved at 55-60°C in 60 ml of absolute ethanol (10% w/v). The solution was filtered under sterile conditions through an 0.2 μ m Nylon 66 filter ($\varnothing = 5$ cm) in approx. 1 min; the filter and filtration apparatus were washed with 10 ml of hot ethanol, which was combined with the rest. The organic solution, maintained under agitation, was dripped into 15 litres of aqueous vehicle containing the other ingredients of the formulation at 25°C in approx. 10 min to give the ingredient in crystalline form in

suspension. The organic solvent was eliminated by evaporation at 60°C for one hour, operating under vacuum, and the suspension was made up to volume with water to readjust the titre of the active ingredient.

An aliquot of said suspension was filtered through an 0.45 µm filter; the solid obtained was washed thoroughly with water and dried at 40°C under vacuum for 24 hours. The product obtained is constituted by BDP monohydrate, as confirmed by the Karl-Fischer test (%H₂O= 3.2%, theoretical value 3.3%) and the calorimeter test. The size distribution of the particles in suspension was determined by laser diffraction (Malvern) after sonication. This type of analysis exploits the diffraction of a laser beam by the particles. The parameter considered is the median volumetric diameter in µm of 10%, 50% and 90% of the particles, expressed as d(v,0.1), d(v, 0.5) and d(v, 0.9) respectively, which is determined by assuming that the particles have a geometrical shape equivalent to a sphere. The result was as follows: d(v, 0.9) = 50 micron, d(v, 0.5) = 10 micron and d(v, 0.1) = 1.8 micron.

After 2 hours the suspension obtained was micronised in a high-pressure Niro Soavi homogeniser at the pressure of 600 bar, for a single cycle of treatment.

The suspension obtained was analysed for particle size distribution with the Malvern technique after sonication. The assay and purity of the BDP in the formulation were determined by liquid chromatography (HPLC), and the residual ethanol content by headspace gas chromatography (HS-GC). The results are set out in Table 1.

Table 1 - Chemical and physical parameters of the BDP aqueous suspension

Description	Micronised suspension
Malvern	
d(v,0.1) µm	0.81
d(v,0.5) µm	2.64
d(v,0.9) µm	5.90
Ethanol residue (HSCC)	0.1% w/w
BDP assay (HPLC)	0.394 mg/ml
Total organates (HPLC)	≤ 0.5%

The formulation prepared according to the process of the invention has
 5 the ideal particle distribution for pulmonary administration, with a residual ethanol content well lower than 2.5% w/w, the maximum tolerated limit in accordance with the International Conference on Harmonisation (ICH) guideline Q 3 C "Impurities: residual solvents" issued in March 1998.

The particle size of the suspension was checked after 1 month of
 10 storage at a temperature below 7°C. No significant crystalline regrowth of the suspended particles was observed under these conditions.

The whole process can be performed under aseptic conditions.

Example 2 - Preparation of an aqueous suspension based on 0.05% (w/v)**budesonide****Composition**

Ingredients	Total quantity of the preparation	Quantity by unit dose
Sterile micronised budesonide	2 g	(1.0 mg)
Polysorbate (Tween) 80	4 g	(2.0 mg)
Disodium edetate dihydrate	2 g	(1.0 mg)
Sodium citrate dihydrate	3.2 g	(1.6 mg)
Citric acid hydrate	0.8 g	(0.4 mg)
Sodium chloride	36 g	(18 mg)
Water for injection q. s. for	4 l	(2.0 ml)

5 Water (4 litres) was loaded in a 6 litres reactor. Sodium chloride (36.0 g) and Tween 80 (4.0 g) were added and the mixture was stirred for 5 minutes at 20-25°C until dissolution was complete. Disodium edetate dihydrate (2.0 g), sodium citrate dihydrate (3.2 g) and citric acid hydrate (0.8 g) were added and the mixture was stirred for 5 minutes at 20-25°C; the final pH was 5.25.

10 Budesonide (2.0 g) was weighed in a 50 ml flask. Ethanol (16 ml) was added and the mixture was heated at 60-70°C until dissolution was complete; the solution was transferred in a filter holder equipped with a nylon 0.2 µm filter.

Nitrogen pressure (0.8 bar) was gradually applied and the filtered solution was collected in a 50 ml dropping funnel. The solution was dropped
15 in the 6 l reactor under vigorous stirring during 15 minutes, and immediate crystallization of budesonide was achieved. The filter and the dropping funnel were washed with ethanol (4 ml) which was dropped in the reactor. The so obtained suspension was stirred for 60 minutes at 20-25°C.

The crude suspension was gradually loaded in a Niro Soavi high-

pressure homogeneizer and micronized under the following conditions: 1st cycle pressure: 150 bar; 2nd cycle pressure: 600 bar. The collected micronized suspension was analysed in comparison to the suspension before has been subjected to the wet micronisation treatment for the following analytical parameters: particle size distribution with the Malvern technique after sonication, budesonide assay, pH. The results are reported in Table 2

Table 2 - Chemical and physical parameters of the budesonide aqueous suspension

Description	Crude suspension	Micronised suspension
Malvern		
d(v,0.1), μm	3.59	1.75
d(v,0.5), μm	7.23	4.19
d(v,0.9), μm	11.54	6.06
pH	5.25	5.35
Budesonide assay (HPLC)	-	0.496 mg/ml

The results show that the active ingredient has a good particle size distribution for pulmonary administration already after crystallisation by using as anti-solvent water and that it can be further improved by a wet micronisation treatment in a high-pressure homogeneizer.

CLAIMS

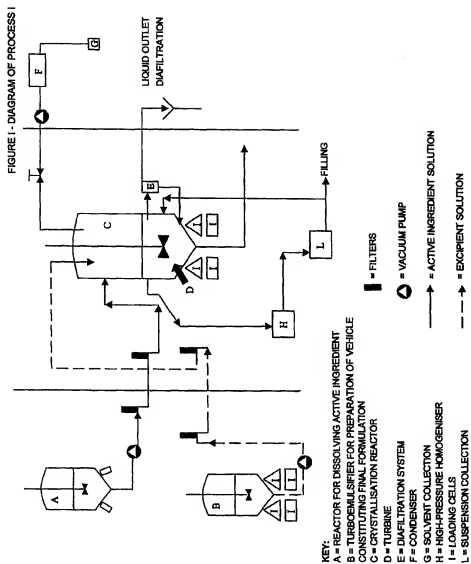
1. Process for the preparation of sterile formulations in the form of aqueous suspensions for pulmonary administration by inhalation comprising a micronised crystalline active ingredient insoluble in water, which comprises the following steps:
 - i) a solution of the active ingredient in an organic solvent is prepared in a suitable reactor (A);
 - ii) said solution is sterilised by filtration;
 - 10 iii) in parallel, a sterile aqueous phase containing suitable excipients is prepared in a turboemulsifier (B);
 - iv) the sterile organic solution ii) is added in a suitable reactor (C) to the sterile aqueous phase iii) to yield the active ingredient in crystalline form so forming a sterile suspension;
 - 15 v) the organic solvent is eliminated.
2. Process as claimed in claim 1, wherein the 90% d(v,0.9) of the particles in suspension has a particle size less than or equal to 60 micron.
3. Process as claimed in claims 1 and 2, wherein the organic solution is maintained at a temperature of between 25 and 80°C.
- 20 4. Process as claimed in claims 1-3 wherein the temperature of the sterile aqueous phase is comprised between 5 and 50°C.
5. Process as claimed in claim 4 wherein the temperature is comprised between 10 and 25°C.
6. Process as claimed in claims 1-5, wherein the time of addition of the organic solution ii) to the sterile aqueous phase iii) is comprised between 1 and 20 minutes.
- 25 7. Process as claimed in claim 6 wherein the time is comprised between 2 and 10 minutes.

8. Process as claimed in claims 1-7, wherein the organic solvent is selected from the group of ethanol, acetone, methyl ethyl ketone and ethyl acetate.
9. Process as claimed in claim 8 wherein the organic solvent is ethanol.
- 5 10. Process as claimed in claims 1-9, wherein the crystalline active ingredient obtained is in the form of a hydrate.
11. Process as claimed in any of the preceding claims, wherein the aqueous suspension is subjected to a wet micronisation treatment in a high-pressure homogeniser (H) to further reduce the particle size of the active ingredient.
- 10 12. Process as claimed in claim 11, wherein said treatment is performed at an operating pressure of between 100 and 1000 bar for one or more cycles of treatment.
13. Process as claimed in claims 11 and 12, wherein the operating pressure is between 150 and 800 bar.
- 15 14. Process as claimed in any of the preceding claims, wherein the sterile aqueous phase contains one or more pharmaceutically acceptable excipients, selected from the group of wetting agents, surfactants, viscosity-increasing agents, stabilising agents, isotonicity agents and/or buffers.
15. Process as claimed in claim 14, wherein the excipient is a wetting agent
- 20 selected from polysorbate 20, sorbitan monolaurate and their mixture.
16. Process as claimed in claims 1-10, subjected to the following additional steps:
- a) isolation and collection of the active ingredient by filtration in a sterile environment;
 - 25 b) reduction of particle size of the active ingredient by dry micronisation in a fluid energy mill (D) operating in a sterile environment;
 - c) transfer of the micronised active ingredient to a turboemulsifier (B)

in which a pre-sterilised aqueous solution containing suitable excipient has been prepared.

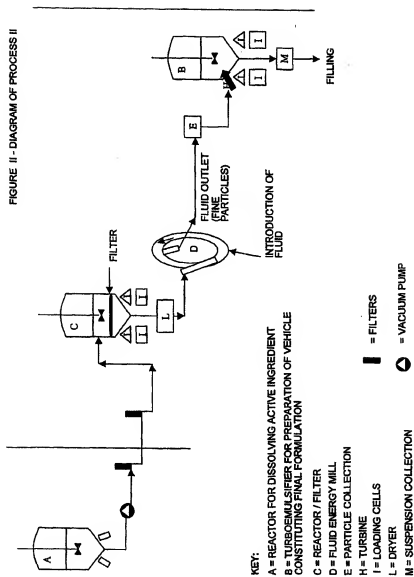
17. Process according to one of the preceding claims, wherein the active ingredient is selected from the group of antibiotics or corticosteroids such as
- 5 BDP, budesonide and its epimers, flunisolide, mometasone furoate, ciclesonide, rofleponide, triamcinolone acetonide and fluticasone propionate.
18. Pharmaceutical formulations for inhalation, under the form of sterile aqueous suspensions of micronised crystalline active ingredients obtained as claimed in any of the preceding claims.
- 10 19. Pharmaceutical formulations as claimed in claim 18, wherein the micronised active ingredient is in hydrated form.
20. Pharmaceutical formulation in the form of sterile aqueous suspensions for pulmonary administration by inhalation comprising as active ingredient micronised crystalline BDP monohydrate wherein at least 90% of the
- 15 suspended particles is less than or equal to 6 micron.

1/2



2/2

FIGURE II - DIAGRAM OF PROCESS II



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14386

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/53901 A (LOUIS OLIVIER ;LLORCA NATHALIE (FR); ROSIER PATRICK (FR); CAVAILLO) 28 October 1999 (1999-10-28) page 8, line 1 - line 21 examples	18-20
X	WO 00/25746 A (BRAMBILLA GAETANO ;BERNINI EVA (IT); CHIESI PAOLO (IT); MALVOLTI C) 11 May 2000 (2000-05-11) cited in the application page 2, line 13 -page 5, line 7 examples 1,2 claims	18

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the International search

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/14386

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/00199 A (THEOPHILUS ANDREW LEWIS ;GLAXO GROUP LTD (GB); SINGH HARDEV (GB)); 3 January 2002 (2002-01-03) cited in the application claim 1; example 1 -----	18
X	WO 02/00198 A (THEOPHILUS ANDREW LEWIS ;GLAXO GROUP LTD (GB); SINGH HARDEV (GB)); 3 January 2002 (2002-01-03) cited in the application claim 1; example 1 -----	18
A	GB 2 107 715 A (GLAXO GROUP LTD) 5 May 1983 (1983-05-05) cited in the application page 1, line 34 - line 46 page 2, line 34 - line 41 examples claims -----	1-20

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/14386

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9953901	A	28-10-1999	AT 228823 T 15-12-2002
			AU 755066 B2 05-12-2002
			AU 3523199 A 08-11-1999
			BR 9909736 A 19-12-2000
			CA 2328882 A1 28-10-1999
			CN 1305369 T 25-07-2001
			DE 69904312 D1 16-01-2003
			DE 69904312 T2 16-10-2003
			DK 1073417 T3 24-03-2003
			EE 200000608 A 15-08-2001
			WO 9953901 A1 28-10-1999
			EP 1073417 A1 07-02-2001
			ES 2189410 T3 01-07-2003
			HR 20000689 A1 28-02-2001
			HU 0101608 A2 28-03-2002
			ID 27887 A 03-05-2001
			JP 2002512183 T 23-04-2002
			NO 20005218 A 10-11-2000
			NZ 507619 A 30-05-2003
			PL 343491 A1 27-08-2001
			PT 1073417 T 30-04-2003
			SI 1073417 T1 31-08-2003
			TR 200100144 T2 21-06-2001
			US 2003157032 A1 21-08-2003
			ZA 200005761 A 17-10-2001
WO 0025746	A	11-05-2000	IT MI982364 A1 03-05-2000
			AU 762367 B2 26-06-2003
			AU 1266600 A 22-05-2000
			BR 9915251 A 30-10-2001
			CA 2349268 A1 11-05-2000
			CN 1335766 T 13-02-2002
			CZ 20011541 A3 12-09-2001
			EA 3228 B1 27-02-2003
			WO 0025746 A2 11-05-2000
			EP 1126823 A2 29-08-2001
			HU 0104230 A2 28-03-2002
			JP 2002528484 T 03-09-2002
			NO 20012175 A 02-07-2001
			NZ 511305 A 25-07-2003
			PL 347908 A1 22-04-2002
			SK 5932001 A3 06-11-2001
			TR 200101209 T2 21-09-2001
			US 6464958 B1 15-10-2002
			ZA 200103526 A 03-06-2002
WO 0200199	A	03-01-2002	AU 6621901 A 08-01-2002
			EP 1294360 A1 26-03-2003
			WO 0200199 A1 03-01-2002
			JP 2004500984 T 15-01-2004
			US 2004045805 A1 11-03-2004
WO 0200198	A	03-01-2002	AU 6621801 A 08-01-2002
			EP 1294359 A1 26-03-2003
			WO 0200198 A1 03-01-2002
			JP 2004500983 T 15-01-2004
			US 2003181432 A1 25-09-2003

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/14386

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2107715	A	05-05-1983	AU 551471 B2 01-05-1986
			AU 8946082 A 03-05-1984
			BE 894725 A1 18-04-1983
			CA 1189853 A1 02-07-1985
			CH 652134 A5 31-10-1985
			DE 3238569 A1 05-05-1983
			DK 168389 B1 21-03-1994
			ES 8404374 A1 16-07-1984
			FI 823561 A ,B, 20-04-1983
			FR 2514769 A1 22-04-1983
			HK 100989 A 29-12-1989
			IE 54170 B1 05-07-1989
			IT 1196553 B 16-11-1988
			JP 1736919 C 26-02-1993
			JP 4024358 B 24-04-1992
			JP 58090599 A 30-05-1983
			KR 8900664 B1 22-03-1989
			MY 91087 A 31-12-1987
			NL 8204013 A 16-05-1983
			NZ 202212 A 24-01-1986
			PT 75692 A 01-11-1982
			SE 454356 B 25-04-1988
			SE 8205904 A 18-10-1982
			US 4866051 A 12-09-1989
			ZA 8207601 A 28-09-1983